(f) a sequence[s] which due to degeneracy of the ~~genetic code~~, encodes the same ~~amino acid~~ sequences as those encoded by the sequences defined under (a), (b), (c) and (d).

Please amend Claim 3 as follows:

3. (Once amended) The vector of Claim 2, characterized in that the nucleic acid is functionally linked to a regulatory sequence[s] which ensures the expression of the nucleic acid in prokaryotic or eukaryotic cells.

Please amend Claim 17 as follows:

17. (Once amended) The regulatory ~~[region]~~ sequence of Claim 3 which naturally controls ~~transcription~~ of [a] the nucleic acid [of Claim 1] in insect cells and ensures [specific] expression thereof.

Please amend Claim 22 as follows:

22. (Amended) The nucleic acid of Claim 1 (c) which ~~comprises~~ a sequence that hybridizes with a sequence defined ~~under~~ (a) in 0.5 x SSC at 60°C.

Please amend Claim 23 as follows:

23. (Amended) The nucleic acid of Claim 1 (c) which comprises the sequence that [hybridized] hybridizes with a sequence defined in (a) in 0.2 x SSC at 60°C.

REMARKS

Priority

Applicants have amended the specification to include the statement that they claim priority for the instant application to German Application no. 19819829.9 filed on May 4, 1998 in accordance with the Examiner's suggestion.

Information Disclosure Statement

A supplemental Information Disclosure Statement is filed herewith to appropriately list the Eastham et al reference initially disclosed on page 2, and again on page 16, of the specification.

Drawings

Applicants submit herewith a revised Figure 1 to comply with the requirements of 37 C.F.R. 1.52 and 1.84 and to remove the basis for the Draftperson's objection.

Specification

Applicants have amended the specification to comply with the preferred layout and content of patent applications as set forth in 37 C.F.R 1.77 and MPEP 608.01(a).

Claim Rejections : 35 U.S.C. § 101

Applicants have followed the Examiner's suggestion and amended Claim 1 to recite "an isolated nucleic acid", which brings the claimed subject matter within the ambit of patentable subject matter. Diamond, Commissioner of Patents and Trademarks v. Chakrabarty, 206 USPQ 193 (US Sup. Ct. 1980).

35 U.S.C. § 112, ¶ 1

Applicants have amended Claim 1 to clarify that the claimed nucleic acid sequence is limited to those encoding insect acetylcholine receptors, complete or partial sequences thereof. All dependent claims are hence also within the scope of the disclosure. Applicants are disclosing and claiming a complete sequence encoding an insect acetylcholine receptor which encompasses sequences having at least 70% homology thereto. From this disclosed sequence, an average routinier would be enabled to deduce sequences which are at least 70% homologous and encode insect acetylcholine receptors without undue experimentation. 70% homologous sequences can be deduced with the aid of computer programs that predict such parameters as melting temperature, and even secondary structure of the DNA sequence complementary to the target molecule, the disclosed DNA sequence.

The ability of a given sequence to encode insect acetylcholine receptor subunits may be determined by relatively simple comparisons to the known encoding sequence. Therefore, even if a 70% homologous sequence were unable to encode insect acetylcholine receptors (as argued in the Office Action), that sequence would not be within be the scope of the claimed invention. The fact that "experimentation" may be complex does not necessarily make it undue, if the art typically engages in such experimentation. In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), see also In re Angstadt, 190 USPQ 214, 219 (CCPA 1976). A disclosure is presumed to be enabling absent evidentiary basis to the contrary to

question its adequacy. Gould v. Mossinghoff, 229 USPQ 1 (DC DC 1985). Mere broad generalizations and allegations are insufficient to support a holding of non-enablement. Ex Parte Goeddel, 5 USPQ2d 1449 (Bd. Pat. App. & Int. 1985).

The only evidentiary basis given for this rejection is the Examiner's opinion that Applicants have not provided sufficient "guidance" as to how one skilled in the art could determine if a material is within the scope of their invention without undue experimentation. Applicants maintain that they need not teach what is well known in the art, regardless of its complexity. Hybritech, Inc. v. Monoclonal Antibodies, Inc., 231 USPQ2d 81, 94 (Fed. Cir. 1986).

35 U.S.C. § 112 ¶ 2

Applicants have amended Claim 1, hence all dependent Claims 2-7, 10, 17 and 22-31, to clarify that the sequences claimed under Claim 1(f) are those nucleic acid sequences that though encoding the same protein or amino acid sequence as SEQ ID NO. 1 , SEQ ID NO. 2, and SEQ ID NO. 3 and their complementary sequences, are different due to the degeneracy of the genetic code, caused by "wobble positions" in the second and third nucleotide of a codon, but encode nonetheless for the same amino acid sequence. Ascertaining these sequences does not pose an undue burden to the skilled artisan since this can be done with the aid of readily available computer software. Thus, Claim 1(f) still refers to nucleic acid sequences as specified by the preamble to Claim 1, and not to amino acid sequences.

Applicants have amended Claim 17 to clarify the meaning of "specific expression" as that which is performed by a regulatory sequence in an expression vector construct, i.e. expression promoter and/or regulator. Claim 1 does not describe such a regulatory sequence as correctly pointed out by the Examiner. Claim 17 is properly dependent upon Claim 3 which does claim a vector for expressing the sequences of Claim 1 comprising the regulatory sequence. The term "specific" has been deleted to make it clearer that the invention being claimed is not limited to "tissue specific" or "species specific" expression. The regulatory sequence ensures expression of the nucleic acid in the construct/vector. The claim is so amended to clarify the metes and bounds of the invention.

Applicants have amended Claims 22 and 23, to recite specifically that the nucleic acid sequence modified is that claimed in Claim 1 (c) to provide the proper antecedent basis for the further limitation of these dependent claims. Claim 23 has been further amended to correct an obvious typographical error. Specifically, "hybridized" has been corrected to "hybridizes". This amendment clarifies the metes and bounds of the subject matter the Applicants regard as their invention.

35 U.S.C. 102(a) and (b)

Applicants respectfully traverse the rejection of Claim 1 under 35 U.S.C 102(a) and (b) as being anticipated by Schulte et al. (1999), or Celniker et al. (1998), or Liao et al. (1998), or Vogel et al. (1998).

Applicants claim priority to German Application 19819829.9 filed on May 4, 1998. Having a priority date of May 4, 1998, Applicants' application antedates the Schulte et al. reference which was published by deposition in GenBank ® in April 19, 1999. Hence, the Schulte et al. reference is not available as prior art with respect to Applicant's claimed invention and does not provide a proper basis for rejection of Applicants' claims under 35 U.S.C. § 102 (a) or (b). (A certified translation of Applicants' priority document will be submitted upon receipt of an indication that Applicants' claims are otherwise in condition for allowance).

It is axiomatic that to properly sustain a rejection under 35 U.S.C. § 102 (a) or (b), each and every element of the claimed invention must be taught in a single prior art reference. W.L. Gore & Associates, Inc. v. Garlock, Inc., 220 USPQ 303 (Fed. Cir. 1983) and In re Arkley, 172 USPQ 524 (CCPA 1972). Applicants' maintain that no single reference cited by the Examiner meets this basic requirement for the reasons set forth below.

The Celniker et al. sequence (GenBank® Accession number AC004326) is cited as having a 100% best local similarity with the nucleotide SEQUENCE ID NO:1 over a stretch of 210 base pair (bp)., the bounds of which were unspecified in the Office Action. Applicants were unable to isolate the cited sequence from the NCBI database using the ENTREZ search algorithm by entering the GenBank® accession number cited.

Assuming arguendo, that this 210 bp area of homology between a *Drosophila melanogaster* (fruit fly) and the Applicant's disclosed sequence exists, there is no stated functionality of this sequence in the database annotations. A 210 bp region of homology does not meet the requirement that a single prior art reference disclose **each and every element** of the instant invention. The 210 bp *D. melanogaster* region cited by the Examiner is but a small fraction of the nearly 3Kb of sequence Applicants are disclosing and claiming in the instant application. Even if the cited sequence encompasses a 14 bp region claimed by Applicants it does not teach **each and every element** of Applicant's invention. Since the sequence cited by the Examiner is not annotated, this *D. melanogaster* region could conceivably encode for a conserved transmembrane region (70 amino acids long) which would be ubiquitous to every membrane-bound protein in the fruit fly and which would not necessarily have functionality as claimed by Applicants. Hence, the Celniker et al. reference is not an anticipating reference under 35 U.S.C. § 102 (a) or (b).

Similarly, the Liao et al. reference (GenBank® Accession number AF045432), encoding for a *Danio rerio* transcription factor in zebrafish, and Vogel et al. reference (GenBank® Accession number Z97178), encoding for a *Beta vulgaris* elongation factor in sugar beet, do not teach **each and every element** of the instant invention. Each cited reference has only 79 and 98 base pairs of homology, respectively, to the instant claimed sequence. Even though they may, arguendo, have 100% homology with a 14 bp section of the instant invention, they fail to teach Applicants' entire sequence and thus do not disclose **each and every element** of Applicants' invention. The Liao et al. and Vogel et al. references do not therefore anticipate the claimed invention.

Hence, Applicants respectfully request withdrawal of the rejection of Claim 1 under 35 U.S.C 102 (a) and (b) as being anticipated by Schulte et al. (1999), or Celniker et al. (1998), or Liao et al. (1998), or Vogel et al. (1998).

35 U.S.C. § 103(a)

Applicants respectfully traverse the rejection of Claims 2-7, and 24-31 under 35 U.S.C. § 103 (a) as being unpatentable over Schulte et al., or Celniker et al., or Liao et al., or Vogel et al., further in view of Ausubel et al.

In order to establish a *prima facie* case of obviousness the burden is on the PTO to establish three basic criteria: (1) some suggestion or motivation to modify the reference or to combine reference teachings; (2) a reasonable expectation of success; and (3) a teaching or suggestion of all the claim limitations. The teachings or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. In re Vaeck, 20 USPQ 2d 1438, (Fed. Cir. 1991) *citing* In re Dow Chemical Co., 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). Applicants respectfully submit that the Examiner has not made out a *prima facie* case of obviousness for the reasons set forth below.

Applicants claim priority to German Application 19819829.9 filed on May 4, 1998. Having a priority date of May 4, 1998 Applicants application antedates the Schulte et al. reference which was published by deposition in GenBank® in April 19, 1999. Hence, Schulte et al. is not available as prior art with respect to Applicants' invention and does not provide a proper basis for rejection under 35 U.S.C. § 103 (a). (A certified translation of Applicants' priority document will be submitted upon receipt of an indication that Applicants' claims are otherwise in condition for allowance).

The Celniker et al. reference as noted *supra* is relied upon for its teaching of a 210 bp region of homology to Applicants' claimed sequence. As noted *supra*, this reference is part of a *D. melanogaster* genomic sequence with no annotation as to its function. Having no annotation as to its function, it could not reasonably suggest Applicant's claimed invention of an acetylcholine receptor subunit complete or partial sequence. Even a completely homologous 14 bp region would not reasonably suggest Applicants' invention, since it does not meet the criteria to suggest **all** the claim limitations. Hence, the Celniker et al. reference does not reasonably meet the criteria to support a *prima facie* case of obviousness.

The Vogel et al. and Liao et al. references similarly do not meet the criteria to reasonably support a *prima facie* case of obviousness since they do not reasonably suggest **all** the claim limitations of Applicants' invention. The Vogel reference discloses a sugar beet sequence for an elongation factor. A sugar beet does not have a nervous system and thus any similarity to Applicants' invention is completely fortuitous and does not rise to a level above "background noise" in similarity, even in its purported 98 bases of 100% homology. The Vogel reference could not reasonably be construed to suggest Applicant's invention and thus does not reasonably support a case of *prima facie* obviousness.

Similarly, the Liao et al. reference discloses a zebrafish stem cell leukemia protein messenger RNA. It could reasonably be surmised that this region is only present in a disease state in zebrafish. There is no motivation whatsoever in the annotations to this sequence or in any teaching of the reference to direct one skilled in the art to arrive at Applicants' invention, even considering the 79 bp 100% homology for which this reference has been cited.

Liao et al. teaches a tenuous 79 bp area of homology, does not provide any suggestion or motivation for arriving at Applicants' invention nor for combining references, and does not teach or suggest all of the claim limitations to arrive at Applicant's nearly 3Kb of insect acetylcholine receptor subunit sequence. The Vogel et al reference teaches a tenuous 98 bp area of homology, does not provide suggestion or motivation for arriving at Applicants' invention nor for combining references, and does not teach or suggest all of the claim limitations to arrive at Applicant's nearly 3Kb of insect acetylcholine receptor subunit sequence. Hence, the Vogel et al. and Liao et al. references do not reasonably support a *prima facie* case of obviousness since they do not meet any of the above cited criteria for a showing of *prima facie* obviousness required of the PTO.

The Ausubel reference cited by the Examiner is a compilation of short protocols in molecular biology. It does not reasonably suggest Applicants' invention in the instant application. Although it discloses general methods used in molecular biology, Ausubel does not provide the guidance necessary to combine the cited references in the manner necessary to "arrive at" Applicants' invention. Even

assuming arguendo, that such motivation exists, the combined teachings of the references would not result in a nucleic acid sequence having **all** of the claimed limitations of Applicants' invention. The 210 bp region of "homology" of Celniker et al., the 79 bp region of "homology" of Liao et al., and the 98 bp region of "homology" of Vogel et al. referred to in the Office Action proposed by the Examiner do not reasonably suggest **all** the claim limitations of Applicant's nearly 3Kb of disclosed sequence. None of the cited references provide the bounds or the areas of homology to Applicants invention and there is not suggestion or guidance as to the order for combining these sequences to "arrive at" Applicant's invention. Furthermore, the cited references do not reasonably suggest a sequence, construct, vector, host cell line, for an acetylcholine receptor subunit because the functions of the cited references do not provide such guidance and they originate in distinct organisms, i.e zebra fish and sugar beet, completely unrelated to insects. Even, the Celniker et al. fruit fly gene proposed by the Examiner does not provide any indication as to its function. Hence none of the cited references support a *prima facie* finding of obviousness of Applicants' invention.

There is thus no reasonable basis for supporting a rejection for *prima facie* obviousness of Applicants' invention because the cited references: fail to suggest or motivate one of reasonable skill in the art to modify the references or to combine reference teachings; the prior art reference, or references when combined, do not teach or suggest all the claim limitations; and the teachings or suggestion to make the claimed combination and the reasonable expectation of success are not both found in the prior art references, but improperly based on Applicants' disclosure.

Furthermore, even assuming arguendo that the Ausubel prior art reference provides motivation to combine the Applicants' novel invention with elements known in the prior art to arrive at a process of, for example, over-expressing the nucleic acids of the instant invention, a known process used to produce a novel product is patentable. In re Pleudemann, 15 USPQ2d 1738 (Fed. Cir. 1991), *see also* In re Durden, 226 USPQ 359 (Fed. Cir. 1985).

As stated by Examiner in the instant Office Action at page 18; "Schulte et al., Celniker et al., Liao et al., and Vogel et al. *fail to specifically teach vectors and host*

cells comprising the various nucleic acids [claimed by Applicants]" (*emphasis added)*. This statement clearly supports Applicants' position that these references do not support a *prima facie* obviousness rejection of their claimed invention.

Applicants therefore respectfully request that the rejection of Claims 2-7, and 24-31 under 35 U.S.C. § 103 (a) as being unpatentable over Schulte et al., or Celniker et al., or Liao et al., or Vogel et al., further in view of Ausubel et al. be withdrawn.

Applicants further courteously request entry of this amendment and allowance of all pending claims.

Respectfully submitted,

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